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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,417	KRIEG, PAUL A.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26, 28-31 and 33-59* is/are pending in the application.

4a) Of the above claim(s) *15-20,31 and 33-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21-26 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26, 28-31 and 33-59 are all the pending claims for this application.

2. Claims 27 and 32 were cancelled in the Reply of 2/13/07.

3. Applicants amendment to the specification to introduce sequence identifiers to [012] and [043] by the Preliminary Amendment of 6/14/04 has been considered and entered.

Election/Restrictions

4. Applicant's election with traverse of Group I (Claims 1-30) in the reply filed on 2/13/07 is acknowledged. The traversal is on the ground(s) that searching each of the four inventive groups would not be a serious burden as each group "relates to the modulation of the activity of the same polypeptide, apelin."

This is not found persuasive because the test for restriction under MPEP 808 is two-pronged: a) a determination that the inventive groups *as claimed* are distinct and b) a showing of a serious search burden if not restricted. Applicants have not addressed with sufficient technical (or legal) arguments the first or second prong of the test, namely, that while each of the groups involves modulating apelin activity, the methods require different reagents and different steps in order to affect a distinct and separate population and to obtain a distinct and separate outcome. Further, searching each of the groups involves text and sequence searching in separate databases. For example, claims in Group I, must be searched not only in commercial amino acid sequence databases, but also in textual databases because isolated polypeptides (i.e., SEQ ID

NOs: 1-5) are often disclosed without the benefit of sequence information although the amino acid sequence is inherently the same as the sequence claimed.

The restriction requirement is still deemed proper and is therefore made FINAL.

5. Claims 31 and 33-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventive Groups II-IV, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 2/13/07.

6. Applicant's election of species A for inhibitors affecting apelin and nested species for antibody to apelin in the reply filed on 2/13/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the election of species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

7. Claims 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species of inhibitors affecting APJ, there being no allowable generic or linking claim.

8. Claims 1-14, 21-26 and 28-30 are all the pending claims under examination.

Information Disclosure Statement

9. The U.S., international and non-patent references filed in the IDS of 1/10/05 have been considered and entered.

Sequence Listing/ New Matter

10. The Preliminary Amendment of 10/7/05 requesting entry of a revised Sequence Listing in order to correct a sequence error in SEQ ID NO: 11 has been considered but not entered. Applicant's statement does not indicate what error has been corrected as between the revised and original Sequence Listing, and where original description support for SEQ ID NO:11 in the revised Sequence Listing of 10/7/05 can be found in the specification, claims or drawings as originally filed. Accordingly, the revised Sequence Listing raises an issue of new matter for SEQ ID NO:11.

Specification

11. The disclosure is objected to because of the following informalities:

a) The use of several trademarks (e.g., endostatin®, angiostatin®) has been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are advised to carefully check the specification for any trademarks that may not be properly identified.

b) The specification is objected to because it does not provide sequence identifiers for the following sequences pursuant to 37 CFR 1.821 (c) and/or (d):

1) KXKR, RXRR, KXXR, and RXXR (p. 14, [043]).

Claim Objections

12. Claim 28 is objected to for omitting to include the term "and" before the final species of the Markush group.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-14, 21-26, and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-14, 21-26 and 28-30 are indefinite for the recitation "inhibiting angiogenesis or tumorigenesis in a biological sample" because in Claim 1, it is not clear where the biological sample is taken from or obtained, and the relevance of inhibiting angiogenesis or tumorigenesis vis-à-vis inhibiting apelin activity in the sample. Is the sample a tissue or organ biopsy from a subject having a disease or disorder associated with angiogenesis or tumorigenesis? What relevance does the inhibitory effect on apelin activity have to the biological sample, and is the determined inhibitory effect on apelin activity in vitro (or ex vivo) intended for extrapolation to treating the subject from which the biological sample was obtained? Claims 1-14 and 21-26 appear to be drawn to a method for screening or predicting sensitivity to apelin-inhibiting drugs using a subject's biological sample, and dependent Claims 28-30 appear to be drawn to treating the

subject with the apelin-inhibiting composition identified in the screening or predicting step of Claim 1. Clarification is requested.

b) Claims 1, 3-14 and 21-30 are indefinite for omitting a method step because in Claim 1 it is not clear what the biological endpoint or readout is for determining the inhibition of angiogenesis or tumorigenesis in the biological sample in using the composition. What if any parameters in the biological sample are evaluated in order to correlate inhibition of apelin activity with inhibiting tumorigenesis or angiogenesis? What apelin activity is specifically measured?

c) Claims 1-14, 21-26 and 28-30 recite the limitation "the sample" in element b) of Claim 1. There is insufficient antecedent basis for this limitation in the claim.

d) Claim 4 is indefinite for the recitation "APJ" because it is not clear what molecule is intended and one cannot determine the metes and bounds of the claim.

e) Claim 14 is indefinite for the recitation "and that interacts with APJ" because it is not clear whether the antibody or the polypeptide is contemplated as interacting with APJ.

f) Claims 24-30 are indefinite for the recitation "wherein the biological sample is in a patient" because in Claim 24, it is not clear what is meant by the sample being in a patient. How can a sample occur or be found within a patient? Further, in the dependent claims 25-30, it is not clear how treating a patient is further limiting to the method of inhibiting angiogenesis or tumorigenesis in a biological sample of generic Claim 1. The accepted meaning of the phrase "biological sample" more generally refers to obtaining a tissue or fluid sample from a subject or patient for analysis or detection. Further, it is not

clear if the generic method of Claim 1 encompasses an ex vivo treatment step on cells which are then administered back into the patient or a screening or drug-susceptibility assay. Clarification is requested.

g) Claims 6 and 30 are objected to because the Markush group recites the species "VEGFs, FGFs" and it is unclear if nested species for the genus of VEGF or FGF is contemplated, and it so, what other species are encompassed. One cannot determine the metes and bounds for the species of "VEGFs" or "FGFs".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

14. Claims 8 and 14 are rejected under 35 U.S.C. 112, first paragraph, as reciting subject matter that is not supported by the disclosure of the specification.

Claim 8 (element f) and 14 are drawn to anti-apelin antibodies or fragments thereof having the properties of a) inhibiting apelin activity and b) binding having at least 80% or at least 90% identity with the polypeptides of SEQ ID NOS: 1 (human preproapelin); 2 (human apelin-36); 3 (human apelin-17); 4 (human apelin-13) and 5 (zebrafish apelin-13).

The specification merely wishes to have apelin antibodies that bind the above peptides but more importantly, the ability of each antibody to inhibit an activity of apelin such as decreasing vascular permeability and interfering with the interaction of apelin

with the APJ receptor. The specification does not describe a single commercial apelin antibody meeting all the limitations of the claims. The specification does not provide any example of an actual reduction to practice for an apelin antibody meeting all the limitations of the claims. It is also well known in the art that modifications to a protein's structure can affect or reduce antibody binding to the protein (For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Thus, even if an apelin antibody were disclosed for any one of the peptides of SEQ ID NOs:1-5, one skilled in the art could not even be assured that the same antibody would recognize a peptide having at least 80% or at least 90% identity with the peptides of SEQ ID NOs:1-5, much less that the antibody would be inhibitory for any apelin activity. Thus one skilled in the art would reasonably conclude that Applicant's were not in possession of the apelin antibodies of Claims 8-14 recognizing the apelin peptides of SEQ ID NOs: 1-5 at the time the application was filed.

15. Claims 8 and 14 are rejected under 35 U.S.C. 112, first paragraph, as reciting subject matter that is not supported by the disclosure of the specification.

Claim 8, element f) is drawn to an apelin antibody or fragment thereof binding to a polypeptide having at least 80% identity to the polypeptides of SEQ ID NOS: 1 (human preproapelin); 2 (human apelin-36); 3 (human apelin-17); 4 (human apelin-13)

and 5 (zebrafish apelin-13). Claim 14 is drawn to an apelin antibody or fragment thereof binding to a polypeptide having at least 90% identity with the polypeptides of SEQ ID NOS:1, 2, 3, 4 or 5.

The specification does not teach or suggest any other apelin-related peptides than those of SEQ ID NOS: 1-5, or the structural motifs for any peptide having at least 80% or at least 90% identity with any of the known apelin peptides. Although the specification teaches that variants can be readily screened, the specification and the claims do not provide any guidance on the structure of the polypeptide and what changes can or can not be made. The peptides of element f) in Claim 8 and Claim 14 are not supported by the specification and the specification does not describe in sufficient detail how one skilled in the art could obtain the peptides or recognize those peptides having apelin activity. The specification does not teach examples of species for those peptides having at least 80% or at least 90% identity to SEQ ID NOS:1-5 and which meet all of the limitations of the claims, namely, that the peptides would be a) antigenic and b) that any antibodies recognizing the peptides would be inhibitory for apelin activity. Thus one skilled in the art would reasonably conclude that Applicant's were not in possession of the peptides of Claim 8, element f) and Claim 14 much less any anti-apelin antibody recognizing the peptides at the time the application was filed.

Enablement

16. Claims 1-14, 21-26, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/Relative Skill in the Art

Claims 1-8 are drawn to a method of inhibiting angiogenesis or tumorigenesis in a biological sample by combining the sample with a composition comprising any apelin activity inhibitor, where the composition decreases vascular permeability in the sample, or interferes with apelin protein or peptide binding to a receptor including APJ, and the composition further comprising an anti-cancer agent such as chemotherapeutic, radiotherapeutic, anti-angiogenesis and apoptosis agents, and anti-angiogenesis agents for inhibiting an angiogenic factor VEGF, FGF, PDGFB, EGF, LPA, HGF, PD-ECF, IL-8, angiogenin, TNF-alpha, TGF-beta, TGF-alpha, proliferin and PLGF. Claims 7-14 are

drawn to the composition comprising an apelin antibody or fragment binding to polypeptides of SEQ ID NO:1-5 or polypeptides having at least 80% or at least 90% identity to the polypeptides of SEQ ID NOs: 1-5. Claims 21-23 are drawn to the composition comprising a pharmaceutical carrier, and the biological sample being from a mammal or a human. Claims 24-30 are drawn to the biological sample being a human, where the composition is administered by the different routes recited in Claim 25, where the patient has a disease associated with angiogenesis or tumorigenesis, where the composition further comprises an anti-cancer agent such as chemotherapeutic, radiotherapeutic, anti-angiogenesis and apoptosis agents, and anti-angiogenesis agents for inhibiting an angiogenic factor VEGF, FGF, PDGFB, EGF, LPA, HGF, PD-ECF, IL-8, angiogenin, TNF-alpha, TGF-beta, TGF-alpha, proliferin and PLGF. In order to practice the invention one skilled in the art would be required to understand screening methods for immunotherapeutics, methods for generating and selecting apelin antibodies, and to be skilled in the practice of clinical treatment of angiogenesis and tumorigenesis in human patients having such disorders and administering immunotherapeutic agents affecting apelin.

Disclosure in the Specification

The specification makes a very general disclosure for compositions comprising apelin antagonists which competitively bind to a downstream or upstream member of the cell membrane component metabolic cascade that includes the apelin polypeptide [0044], and for compositions inhibiting apelin activity indirectly, such as a specific endopeptidase and "belonging to the subtilisin family of serine proteases (Barr, 1991,

Cell 66:1-3)" [0045] which putatively cleave apelin to the 13 amino acid and 17 amino acid peptides. Other apelin antagonists are antibodies and fragments thereof [0027]. Example 5 discloses inhibiting vascular growth or angiogenesis in a frog embryo with antisense DNA for apelin. Example 6 of the specification teaches apelin expression was increased in approximately one third of 154 human tumor samples compared to non-tumor tissue based on dot-blot hybridization analysis with labeled cDNA probe for human apelin. Example 7 discloses that upregulation of apelin under hypoxic conditions in primary rat cardiomyocte cells strongly suggest that apelin plays a role in tumor angiogenesis. The specification does not disclose any working example of an inhibitor for apelin activity in a cell line or animal model recognized in the art as a correlate for angiogenesis or tumorigenesis. The specification does not disclose that any apelin activity inhibitor could block angiogenesis or tumorigenesis in a biological sample. The specification does not disclose a model showing that any apelin activity inhibitor much less the instant claimed apelin antibodies could be administered to a human patient in order to inhibit angiogenesis or tumorigenesis. The specification does not reasonably provide enablement for inhibiting angiogenesis or tumorigenesis with just any inhibitor of apelin activity in a biological sample much less any antibody recognizing apelin peptides of SEQ ID NOs:1-5 or peptides having at least 80% or at least 90% identity with the peptides of SEQ ID NOs:1-5, or treating any human patient having an angiogenesis- or tumorigenesis-associated disorder with any apelin inhibitor much less any one of the apelin antibodies. The specification is not enabling for the breadth and scope of the instant claimed invention. Therefore, it appears that undue experimentation would be

required of one skilled in the art to practice the instant invention using the teachings of the specification alone because the specification fails to enable the use of any apelin activity inhibitor for angiogenesis therapy or tumor therapy in a biological sample much less a human patient.

A) Prior Art Status of Immunotherapeutics/Unpredictability of Antibody Therapy in Treating Tumors and Angiogenesis/Undue Experimentation

The use of antibody immunotherapy for the treatment of tumors has been shown to have limitations. Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American July 1994). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to

reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction). Results obtained under controlled conditions and in inbred animals, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

The specification does not disclose whether the method is effective in animals with pre-existing tumor, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the method steps, especially the treatment of pre-existing tumor or tumorigenesis, is underscored by Gura et al (Science Vol 278 11/97 1041-1042) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors

in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in humans patients.

Although antibodies have been shown to have specificity for several tumor antigens and antigens associated with angiogenesis in tumors (Traschel et al. Adv. Drug Delivery Rev. 58:735-754 (2006)), and monoclonal antibodies have been able to induce various degrees of tumor immunity for some diseases, no examples are provided in the application of antibodies as part of immunotherapy to human angiogenesis or tumorigenesis, and it is not clear from the specification whether apelin antibodies binding peptides of SEQ ID NOs:1-5 can generate anti-angiogenesis or anti-tumor responses to all tumors, in all species and to what degree. Further, it is less clear how relevant the anti-zebrafish apelin antibodies binding to a peptide of SEQ ID NO:5 and peptides having at least 80% or at least 90% identity to SEQ ID NO:5, would be in practicing the instant claimed methods. Further, it is not apparent why one skilled in the art would even consider practicing the generic method of Claim 1 with an anti-zebrafish apelin antibody.

As evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on

the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the apelin antibodies of the claimed composition so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

Therefore, due the unpredictability of immunotherapeutics in general, as evidenced by Jain, Chatterjee, Dermer, Gura, Traschel, and Seaver, and in view of the insufficient guidance and/or working examples concerning the use of apelin inhibitors and making/using of the claimed antibodies as immunotherapeutic agents, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer any apelin activity inhibitor or the anti-apelin antibodies for the treatment of any disease and its accompanying pathologies, including angiogenesis and tumorigenesis without undue experimentation.

B) Prior Art Status of Protein Modification/ Unpredictability of Antibody binding to Undefined Protein Variants/Undue Experimentation

Claims 8 (element f) and Claim 14 encompass inoperative apelin polypeptides as discussed supra under section 16, which the skilled artisan would not know how to use much less antibodies drawn to the same (see discussion under section 15, supra). Knowledge of one apelin structure and function does not provide predictability about function of a structurally related protein, even within the same class.

There are no working examples of polypeptides less than 100% identical to the polypeptide SEQ ID NOs:1-5. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification. Even if

the claimed polypeptides had a function. the specification does not provide guidance for using polypeptides related to (*i.e.*, 80% or 90% identity) but not identical to SEQ ID NO:1-5. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

It is well known in the art that even a single modification or substitution in a protein sequence can alter the proteins function. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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